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13. ABSTRACT (Maximum 200 words)

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Abstract

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I. Introduction

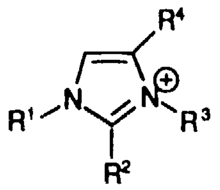
Development of prophylactic and therapeutic agents to prevent and/or treat the lethal and incapacitating effects of organophosphorus (OP) acetylcholinesterase (AChE) inhibitors remains of significance in view of the relative facility with which the OP agents can be prepared and used. The existing strategy employs carbamate type prophylactic agents and anticholinergic and anticonvulsant treatment agents. Pyridostigmine is the current prophylactic agent. Pyridostigmine and related carbamates, including physostigmine, are believed to function as reversible carbamoylating agents at the nucleophilic serine site of AChE. While reducing AChE activity, these drugs are subject to hydrolysis which permits reactivation of the active site, in contrast to the OP agents which are irreversibly bound by the process of partial hydrolysis called "aging".[1] Reactivating agents such as HI-6 are believed to function as dephosphorylating agents although they may also have allosteric effects in view of their *bis*-quaternary structures.[2]

The recent determination of the AChE structure has permitted new insight into the mechanism of action of the enzyme.[3a] In particular, the recognition of the "aromatic gorge" and some of the features of binding of cationic structures provides a previously unavailable structural basis for evaluation of potential prophylactic and therapeutic agents.[3b,3c]

The current work originated with the recognition that certain carbamates of heteroaromatic quaternary salts had prophylactic activity.[4] During the current year we have continued to explore compounds of this type. We have completed, at least for the time-being, work on a series of ω-carbamoyloxyalkyl derivatives of imidazole. We have also undertaken the systematic exploration of derivatives of imidazo[1,2-a]pyridinium salts. These compounds are structurally comparable to physostigmine, but like pyridostigmine are quaternary salts.

II. New Compounds Submitted

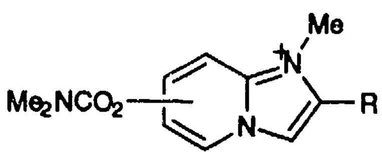
During the first half of the report period primary attention was given to completing the series of 1-, 2- and 4-substituted (ω-carbamoyloxyalkyl)imidazoles. This series includes nine N,N-dimethylcarbamoyloxy derivatives and four of the corresponding N-methylcarbamates were also prepared. The monomethyl carbamate of N,N-dimethyl-3-hydroxy-$\Delta^{3,4}$-piperidinium was also submitted.



	R^1	R^2	R^3	R^4
1	$(CH_2)_nO_2CNMe_2$	H	CH_3	H
2	$(CH_2)_nO_2CNHMe$	H	CH_3	H
3	CH_3	$(CH_2)_nO_2CNMe_2$	CH_3	H
4	CH_3	$(CH_2)_nO_2CNHMe$	CH_3	H
5	CH_3	H	CH_3	$(CH_2)_nO_2CNMe_2$

a: n = 1, **b**: n = 2, **c**: n = 3

Attention was then turned to the imidazo[1,2-a]pyridinium series. Previously we had prepared several 6-carbamoyloxy derivatives. The current objective is to complete this series by preparing all the 5-, 6-, 7- and 8-carbamates with R = H, CH_3, $CH(CH_3)_2$ and Ph.

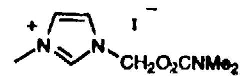
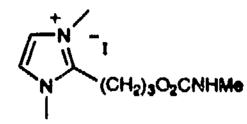
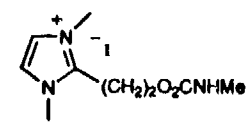
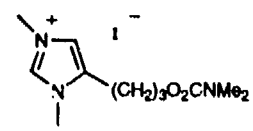
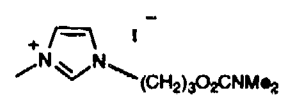
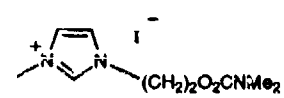
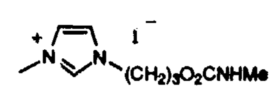
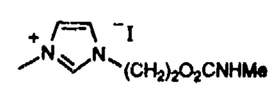
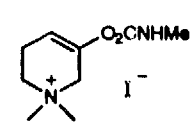


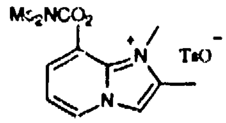
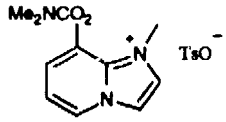
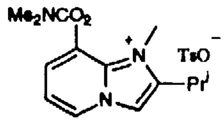
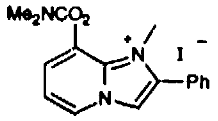
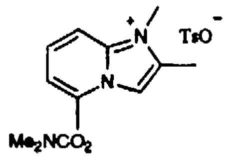
a: R = H, **b**: R = CH_3, **c**: R = $CH(CH_3)_2$, **d**: R = Ph

7	5-carbamate
8	6-carbamate
9	7-carbamate
10	8-carbamate

During the present period we have prepared **7b**, **8c**, and **10a-d**. Compound **8d** had been prepared earlier under contract DAMD17-89-C-9014. The newly prepared compounds are listed in Table I.

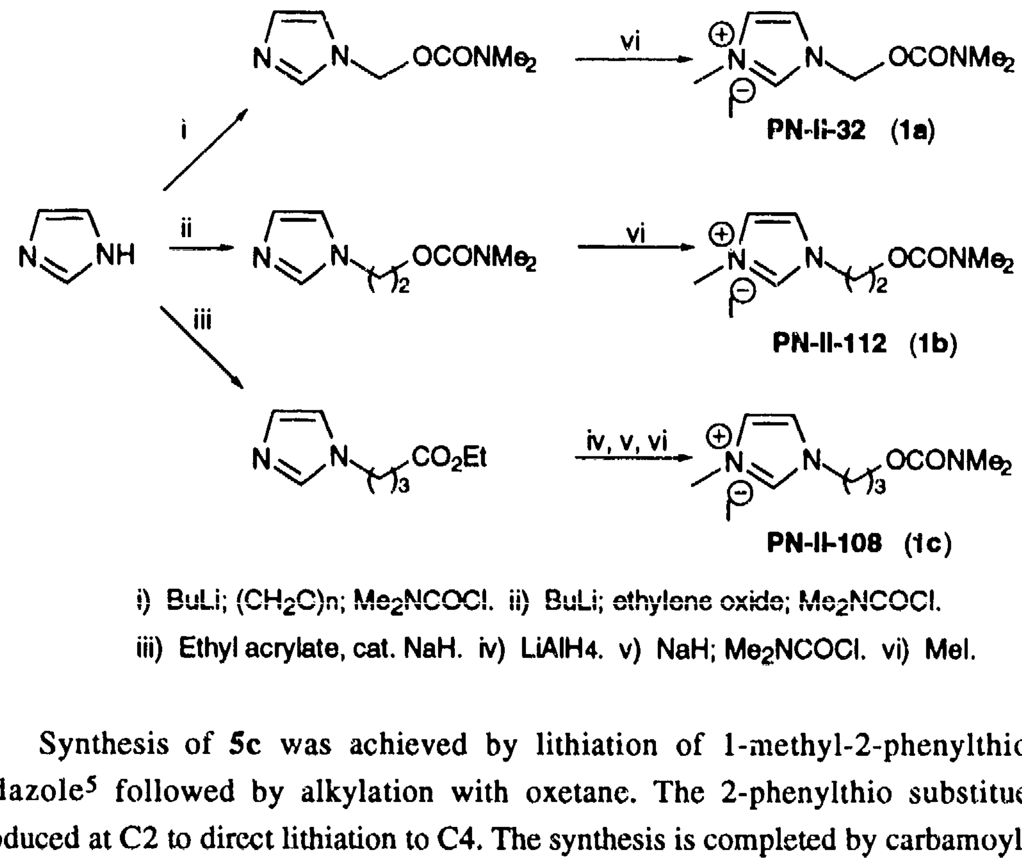
Table 1. New Compounds Submitted

Our sample Number	WRAIR Bottle Number	WR Number	Date of Submission	Structure
PN-II-32	BM 18957		17-8-93	
PN-II-62	BM 18966		17-8-93	
PN-II-68	BM 18975		17-8-93	
PN-I-292	BM 19070		15-9-93	
PN-II-108	BM 19089		15-9- 93	
PN-II-112	BM 19098		15-9-93	
PN-II-178	BN 34803		12-13-93	
PN-II-184	BN 34812		12-13-93	
PN-II-198	BN 34821		12-13-93	

Our sample Number	WRAIR Bottle Number	WR Number	Date of Submission	Structure
PN-II-222	BN 34830		12-13-93	
PN-II-278	BN 36049		3-15-94	
PN-III-28	BN 36058		3-15-94	
PN-II-258	BN 36030		3-15-94	
PN-III-190			6-15-94	

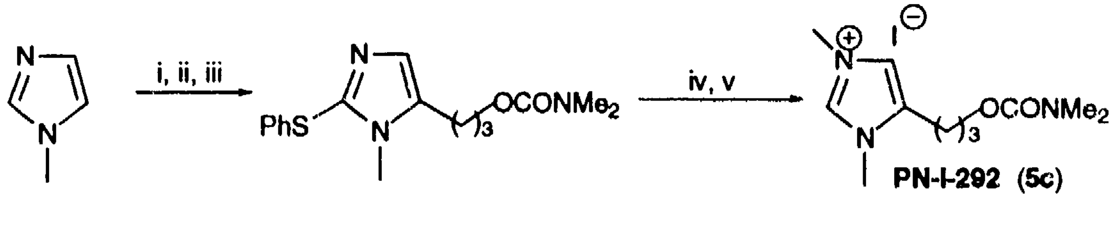
Synthetic Methods

The 1-substituted compounds **1a**, **1b** and **1c** were prepared by homologation of imidazole through its lithium salt by reaction, respectively, with formaldeyde, ethylene oxide or ethylene carbonate and ethyl acrylate. The latter product was then reduced with $LiAlH_4$. Each of the primary alcohols was then carbamoylated and quaternized. The monomethyl carbamates **2b** and **2c** were also prepared using methyl isocyanate.



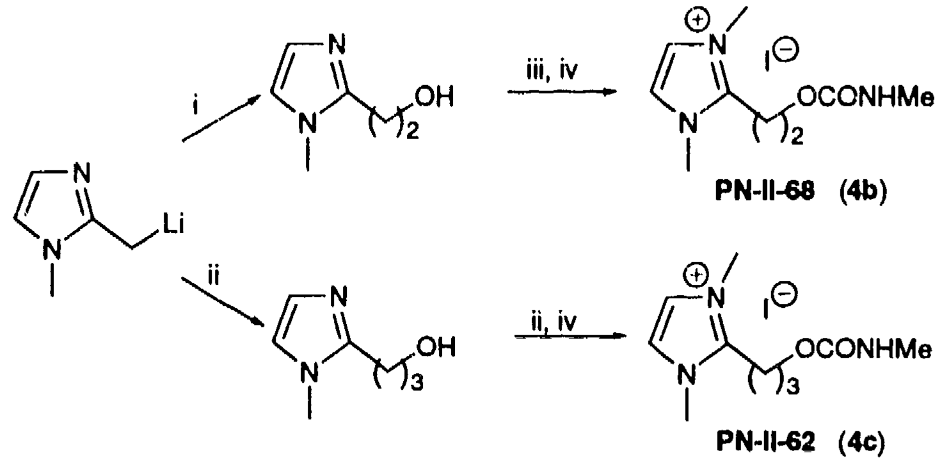
i) BuLi; $(CH_2O)n$; Me_2NCOCl. ii) BuLi; ethylene oxide; Me_2NCOCl.
iii) Ethyl acrylate, cat. NaH. iv) $LiAlH_4$. v) NaH; Me_2NCOCl. vi) MeI.

Synthesis of **5c** was achieved by lithiation of 1-methyl-2-phenylthio-1*H*-imidazole[5] followed by alkylation with oxetane. The 2-phenylthio substituent is introduced at C2 to direct lithiation to C4. The synthesis is completed by carbamoylation, desulfurization and quaternization.



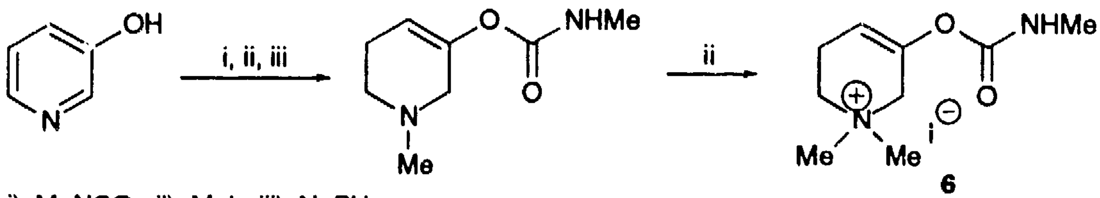
i) BuLi, $(PhS)_2$, THF, -78 °C. ii) BuLi, THF; oxetane, BF_3-Et_2O, -78 °C → rt.
iii) NaH, $ClCONMe_2$, DMF. iv) Raney Ni, EtOH, rt. v) MeI, THF, 75 °C.

The 2-subsituted monocarbamates **4b** and **4c**, were prepared from 1,2-dimethylimidazole which was lithiated[6] at C2 and then homologated with either formaldehyde or ethylene oxide. The resulting primary alcohols were carbamoylated using methyl isocyanate catalyzed by di-*n*-butyltin acetate and then quaternized.



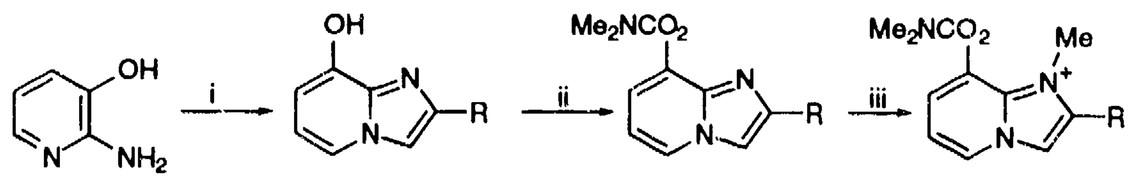
i) $(CH_2O)_n$,THF. ii) Ethylene oxide, THF. iii) MeNCO, $Bu_2Sn(OAc)_2$,CH_2Cl_2. iv) MeI, THF.

We also prepared the monomethyl carbamate **6** of N,N-dimethyl-3-hydroxy-$\Delta^{3,4}$-piperidinium by reducing the N-methylcarbamte of 3-hydroxypyridine and then quaternizing the enol carbamate.



i) MeNCO. ii) MeI. iii) $NaBH_4$.

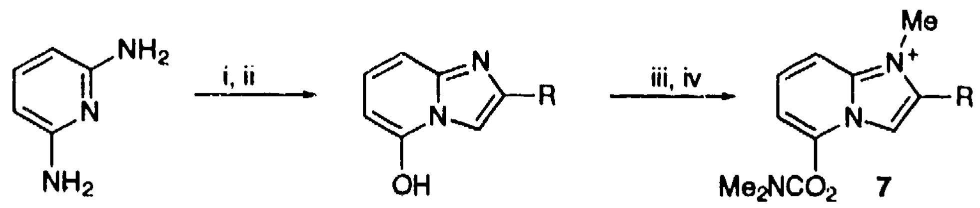
The 8-substituted imidazo[1,2-a]pyridinium salts were prepared beginning with commercially available 2-amino-3-hydroxypyridine. Cyclization can be achieved with chloroacetaldehyde, chloroacetone, 1-bromo-3-methyl-2-butanone[7] or phenacyl bromide, respectively, to obtain the corresponding 2-substituted 8-hydroxyimidazo[1,2-a]pyridines. These were then carbamoylated and quaternized to give **10a-d**.



10 a R = H
b R = Me
c R = Pr^i
d R = Ph

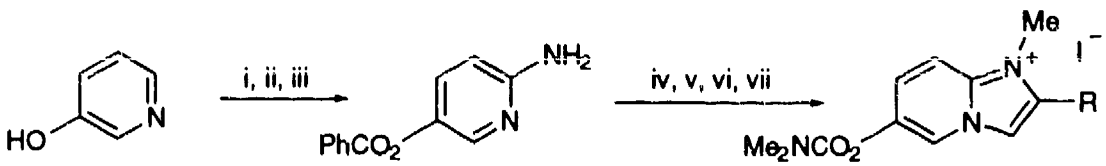
i) $RCOCH_2X$, Δ. ii) $ClCONMe_2$, pyridine, Δ. iii) MeOTs or MeI.

The 5-substituted derivatives **7a-d** are being prepared starting with 2,6-diaminopyridine. It cyclizes with the α-halocarbonyl compounds to give 5-aminoimidazo[1,2-a]pyridines. The amines are converted to 5-hydroxy derivatives with 70% H_2SO_4. The 5-hydroxyimidazo[1,2-a]pyridines exist as the keto tautomer. The carbamoylation must be done under basic conditions. To date the synthesis of **7b** has been completed and preparation of **7a**, **7c** and **7d** is in progress.



i) α-Haloketone, Δ. ii) 70% H_2SO_4, Δ. iii) NaH, DMF; $ClCONMe_2$. iv) MeOTs or MeI.

The route to 2-(2-propyl)-6-hydroxyimidazo[1,2-a]pyridine was developed earlier. It consists of diazo coupling of 3-hydroxypyridine with *p*-nitroaniline, followed by reductive cleavage to give the required starting material 2-amino-5-hydroxypyridine.



8c, d

i) *p*-Nitroaniline, $NaNO_2$. ii) PhCOCl. iii) NaH_2PO_2, Pd/C. iv) α-Haloketone. v) NaOH. vi) Me_2NCOCl, C_5H_5N, Δ. vii) MeI.

Its cyclization with α-haloketone gives the corresponding imidazo[1,2-a]pyridine derivatives. We have not yet begun work on the 7-substituted series (**9**).

IV. Biological Results

Table 2 gives the IC_{50} values[8] measured by determining the concentration dependence of inhibition of electric eel acetylcholinesterase by the various compounds. All available data is included to serve as a basis for comparison.

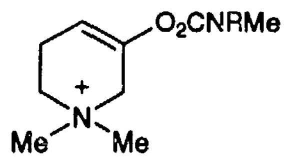
Table 2 Inhibition of Acetylcholinesterase

Compound	Our sample No	WRAIR Bottle No	IC_{50} (μM)
1a	PN-II-32	BM 18957	>100
1b	PN-II-112	BM 19098	>100
1c	PN-II-108	BM 19089	>100
2b	PN-II-184	BN 34812	>100
2c	PN-II-178	BN 34803	>100
3a	DD-II-61	BM 03698	29.1-33.0
3b	PN-68	BM 16186	19.3-21.1
3c	PN-38	BM 16177	25.8-29.9
4a	JC-I-72A	BM 02646	12.3-12.9
4b	PN-II-68	BM 18975	12.4-15.0
4c	PN-II-62	BM 18966	65.0-65.6
5a	PN-177	BM 17816	>100
5b	PN-294	BM 17843	72.9-74.0
5c	PN-I-292	BM 19070	39.0-41.7
	PN-I-226	BM 17825	0.16-0.2
6	PN-II-198	BN 34821	0.14
	PN-236	BM 17834	13.3
10b	PN-II-222	BN 34830	0.16
Pyridostigmine Bromide			0.6-1.0

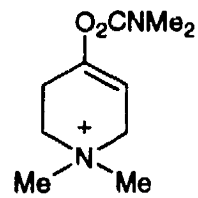
Table 3. *In Vivo* Data for BM03698 and BM02646

		Per Cent Survival		
	Dose	t - 60 min	t - 15 min	t + 10 min
BM03698	6.25	30	50	40, 50
	25	90	100	100, 70
	100	100	90	80, 20
BM02646	6.25	90	90	70, 50
	25	90	100	90, 80
	100	100	90	80, 60

In the ω-carbamoyloxyalkylimidazole series the 1-substituted series **1a-c** and **2b**, **2c** appears to be inactive. The 2-substituted compounds show modest activity with IC_{50} values of 12-65 μM. For the 4-substituted series **5a-c** the activity appears to be increasing with increasing chain length but only reaches marginal levels at n = 3. In *in vivo* data obtained previously (Table 3), both **3a** and **4a** has shown promising prophylactic and antidotal activity. No *in vivo* data is available on the other compounds.



R = H **PN-II-198**
R = Me **PN-226**



PN-236

The enolcarbamates PN-I-226 and PN-236 appear to be very potent AChE inhibitors. The 4-substituted analog PN-236 is only modestly active. No *in vivo* data is available.

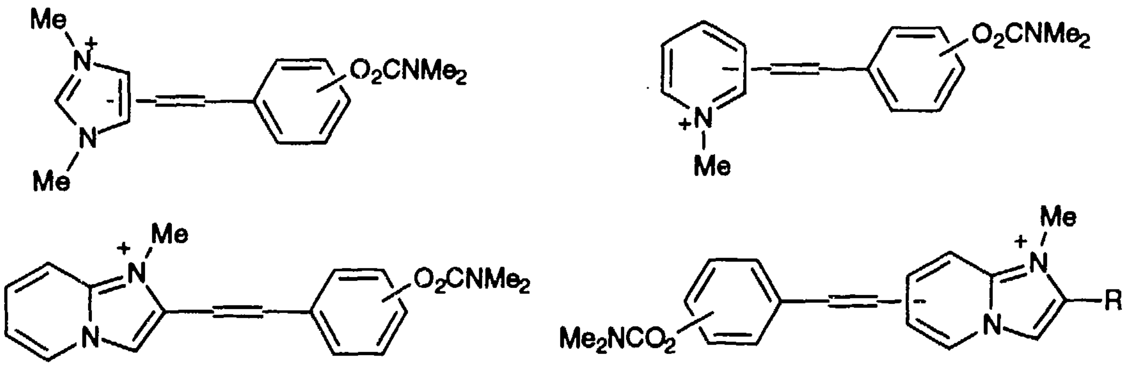
Of the imidazo[1,2-a]pyridines, only **10b** (PN-II-222) has been tested. It shows good *in vitro* activity.

V. Plans for Future Work

Our immediate objective is to complete the carbocyclic carbamates of the imidazo[1,2-a]pyridine series. This requires a workable synthesis of 7-hydroxy-imidazo[1,2-a]pyridines. This substitution pattern is rare. The potential precursors, 4-hydroxy-2-aminopyridine is not easily available[9] We have explored in a preliminary way novel syntheses of this substitution pattern without success. It may be necessary to resort to synthesis of 7-methylimidazo[1,2-a]pyridine and use the methyl group as a basis for introduction of the hydroxyl substituent either via an aldehyde intermediate (Baeyer-Villiger) or the carboxylic acid (Curtius then diazotization).

The mechanism of action of the heteroaromatic carbamates prepared in this work must be presumed to be similar to that of the classical agents such as pyridostigmine. The unique structural feature of the compounds is the fact that the center of positive charge and the carbamate group are further apart than in the natural substrate acetylcholine or in classical carbamates such as pyridostigmine and neostigmine. This more extended separation is compatible with the reinterpretation of the AChE active site which has resulted from the X-ray structure determination.[3a] The structure indicates there is not literally an "anionic" site at the active site but rather that both a diffuse anionic surface charge and a charge gradient directed toward the active site are present. These results suggest there need not be a specific separation of the hydrolyzable group and the charge.

With this structural background we propose to continue to explore compounds in which the two sites are further separated. For example we plan to prepare styryl derivatives of imidazole, pyridine and imidazo[1,2-a]pyridine.



The synthetic methodology to prepare such compounds is available. In addition to exploring the effect of the increased separation on *in vivo* activity, it will be of interest to compare the *in vitro* hydrolytic reactivity of these compounds to the analogs in which the positive charge is closer to the carbamate. One would expect some acceleration of hydrolysis in the compounds with nearby charges as the results of polar effects. It will be of interest to determine if this factor has any biological significance.

The enolcarbamates PN-II-198 and PN-226 are interesting and novel structures. Like aryl carbamates, they should have relatively high activity as carbamoylating agents. Few enol carbamates have been prepared and a number of other structures analogous to muscarinic and nicotinic cholinergic agents would be interesting to prepare.

VI Experimental Section

Melting points are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Georgia. ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75.5 MHz, respectively. Reactions which required anhydrous conditions were carried out under an Ar atmosphere in oven- or flame-dried glassware. Organic solvents were purified by standard techniques prior to use unless used for extractions. All reagents were the best grade commercially available and were used without further purification, unless otherwise noted. 1-Methyl-2-phenylthio-1*H*-imidazole[5] and 1-bromo-3-methyl-2-butanone[7] were prepared according to the known procedure. All intermediates were used in the next steps without further purification, unless otherwise noted.

1-[(N,N-Dimethylcarbamoyloxy)methyl]-1*H*-imidazole (11a)

To a cooled solution (-15 °C) of imidazole (6.81 g. 0.1 mol) in dry THF (130 mL) was added dropwise a solution of *n*-BuLi in hexane (44 mL, 0.11 mol). The mixture was stirred at -10 °C for 30 min then predried paraformaldehyde (4.5 g, 0.15 mol) was added in small portions. After being stirred at -5 °C for 10 min the cooled bath was removed and the reaction mixture was stirred at room temperature overnight. N,N-dimethyl-carbamyl chloride (1.38 mL, 0.15 mol) was added and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with dilute aqueous HCl solution then extracted with ether (3 x 50 mL). The aqueous layer was basified with 20% NaOH solution and extracted with CH_2Cl_2 (4 x 70 mL). The organic layers were washed with H_2O (30 mL), brine (30 mL) and dried (Na_2SO_4). Removal of solvent gave a crude product which was purified by column chromatography (silica gel, $CHCl_3$-MeOH, 9:1) to give **11a** (12.4 g, 73%) as an off-white solid from EtOAc/hexane; mp 72-73 °C; R_f = 0.48 ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 7.72 (s, 1 H), 7.14 (s, 1 H), 7.04 (s, 1 H), 5.86 (s, 2 H), 2.91 (s, 3 H), 2.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.74, 138.09, 129.57, 119.51, 68.36, 36.36, 35.71. Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.55; N, 24.92. Found: C, 49.72; H, 6.52; N, 24.92.

1-[2-(N,N-Dimethylcarbamoyloxy)ethyl]-1*H*-imidazole (11b)

To a cooled solution (-40 °C) of imidazole (6.8 g, 0.1 mol) in dry THF (200 mL) was added slowly a solution of *n*-BuLi in hexane (45.8 mL, 0.11 mol). The mixture was stirred for 30 min and cooled ethylene oxide (10 mL, 0.2 mol) was added at once via canula. The reaction mixture was stirred at room temperature overnight and then N,N-dimethylcarbamyl chloride (13.8 mL, 0.15 mol) was added. After being stirred at room temperature overnight the mixture was quenched with 100 mL of cold water. Organic solvent was removed under aspirator pressure. The aqueous mixture was saturated with NaCl, then extracted with $CHCl_3$ (5 x 100 mL). The organic layers were washed with brine, dried (Na_2SO_4) and filtered. Removal of solvent to dryness gave a yellow solid.

Purification of the crude product by column chromatography (silica gel; $CHCl_3$-MeOH, 19:1) gave **11b** (14.4 g, 79%) as a white solid from EtOAc/hexane: mp 80 - 81 °C; R_f = 0.36 ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 7.51 (s, 1 H), 7.07 (s, q H), 6.96 (s, 1 H), 4.33 (t, 2 H, J = 5.2 Hz), 4.21 (t, 2 H, J = 5.2 Hz), 2.91 (s, 3 H), 2.86 (s, 3 H). Anal. Calcd for $C_8H_{13}N_3O_2$: C,52.45; H, 7.15; N, 22.94. Found: C, 52.38; H, 7.18; N, 22.83.

Ethyl 3-(Imidazol-1-yl)propionate (12)

A mixture of imidazole (6.8 g, 0.1 mol) and NaH (48 mg, 2 mmol) in dry THF (100 mL) was stirred for 15 min at room temperature. Ethyl acrylate (13 mL, 0.12 mol) was then added at once. After being stirred at 60 °C for 2 days, the reaction mixture was cooled in an ice bath and quenched with water. The organic solvent was removed under aspirator pressure. The aqueous mixture was basified with aqueous 20% NaOH solution to pH=11, saturated with NaCl and then extracted with CH_2Cl_2. The organic layers were washed with brine, dried (Na_2SO_4) and filtered. Removal of the solvent to dryness gave a dark yellow liquid. Purification of the crude product by column chromatography on silica gel ($CHCl_3$-MeOH, 9:1) gave **12** (14.7 g, 87%), a very pale yellow liquid: R_f = 0.39 ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 7.51 (s, 1 H), 7.04 (s, 1 H), 6.94 (s, 1 H), 4.27 (t, 2 H, J = 6.6 Hz), 4.14 (q, 2 H, J = 7.2 Hz), 2.77 (t, 2 H, J = 6.6 Hz), 1.24 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 170.34, 137.12, 129.50, 118.68, 60.96, 42.14, 35.87, 13.94.

1-(3-Hydroxypropyl)-1*H*-imidazole (13)

To an ice-cooled mixture of $LiAlH_4$ (0.9 g, 23.8 mmol) in THF (30 mL) was added dropwise a solution of **12** (2 g, 11.88 mmol) in THF (5 mL). After 10 min the ice-bath was removed and the mixture was stirred at room temperature for 2 h. The reaction mixture was then cooled in an ice bath and sequentially quenched with water (0.9 mL), 20% NaOH solution (0.8 mL) and water (2.7 mL). The mixture was filtered with the aid of Celite. The filtered cake was washed thoroughly with hot THF. Evaporation of the solvent to dryness gave **13** (1.5 g, 100%) as a colorless liquid: R_f = 0.12 ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 7.46 (s, 1 H), 7.04 (s, 1 H), 6.93 (s, 1 H), 4.12 (t, 2 H, J = 6.7 Hz), 3.60 (t, 2 H, J = 5.7 Hz), 1.99 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.39, 129.12, 118.91, 57.99, 43.35, 33.28.

1-[3-(N,N-Dim^thylcarbamoyloxy)propyl]-1*H*-imidazole (11c)

A solution of N,N-dimethylcarbamoyl chloride (0.71 mL, 7.72 mmol) in THF (3 mL) was added dropwise to a slurry mixture of **13** (0.65 g, 5.15 mmol) and NaH (0.17 g, 7.0 mmol) in THF (12 mL) at reflux temperature. The reaction mixture stirred at that temperature for 6 h, and was then cooled to room temperature, quenched with water (15 mL), basified to pH=10, saturated with NaCl and extracted with $CHCl_3$ (4 x 30 mL). The organic layers were washed with brine (30 mL), dried (Na_2SO_4) and filtered. Removal of the solvent gave a brown liquid. Column chromatography (silica gel, $CHCl_3$-MeOH, 9:1) of the crude product gave **11c** (0.71 g, 69%) as a colorless liquid: $R_f = 0.40$ ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 7.48 (s, 1 H), 7.05 (s, 1 H), 6.94 (s, 1 H), 4.03-4.10 (m, 4 H), 2.90 (s, 6 H), 2.07-2.16 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 155.85, 136.81, 129.24, 118.51, 61.52, 43.50, 36.12, 35.54, 30.38. Anal. Calcd for $C_9H_{15}N_3O_2.2/3H_2O$: C, 51.66; H, 7.86; N, 20.08. Found: C, 51.35; H, 7.86; N, 19.93.

1-[2-(N-Methylcarbamoyloxy)ethyl]-1*H*-imidazole (14)

To an ice-cooled solution of 1-(2-hydroxyethyl)-1*H*-imidazole[10] (3.48 g, 31 mmol) and methyl isocyanate (5.5 mL, 93 mmol) in dry CH_2Cl_2 (10 mL) were added a few drops of $Bu_2Sn(OAc)_2$. The mixture was stirred at room temperature for 2 h and the solvent was evaporated to dryness to give a crude yellow solid. Purification of the crude product by flash column chromatography on silica gel ($CHCl_3$-MeOH, 9:1) afforded **14** (4.48 g, 85%) as a white solid from EtOAc: mp 121.5-122.5 °C; $R_f = 0.37$ ($CHCl_3$-MeOH, 9:1); IR (KBr)$_{vmax}$ 3115, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (s, 1 H), 7.04 (s, 1 H), 6.94 (s, 1 H), 5.68 (br s, 1 H), 4.31 (t, 2 H, J = 5.1 Hz), 4.17 (t, 2 H, J = 5.1 Hz), 2.77 (d, 3 H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 156.35, 137.34, 129.30, 118.97, 63.30, 46.21, 27.30. Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55: N, 24.84. Found: C, 49.79; H, 6.59; N, 24.88.

1-[3-(N-Methylcarbamoyloxy)propyl]-1*H*-imidazole (15)

Carbamoylation of **13** (2.16 g, 16.64 mmol) with methyl isocyanate (2.97 mL, 50 mmol) as described for **14** gave a thick oil. Purification of the crude product by column chromatography on silica gel ($CHCl_3$-MeOH, 9:1) gave **15** (3.07 g, 98%), as white crystals from EtOAc/hexane: mp 61-62.5 °C; $R_f = 0.24$ ($CHCl_3$-MeOH, 9:1); IR (KBr)$_{vmax}$ 1079 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (s, 1 H), 7.05 (s, 1 H), 6.93 (s, 1 H), 5.39 (br s, 1 H), 4.02-4.08 (m, 4 H), 2.78 (d, 3 H, J = 5.1 Hz), 2.04-2.12 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 156.74, 136.95, 129.25, 118.67, 60.93, 43.49, 30.48, 27.24. Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.93. Found: C, 52.29; H, 7.17; N, 22.77.

1-Methyl-2-[2-(N-methylcarbamoyloxy)ethyl]-1*H*-imidazole (16b)

1-Methyl-2-(2-hydroxyethyl)-1*H*-imidazole[11] (3.4 g, 26.9 mmol) was carbamoylated with methyl isocyanate (8 mL, 134 mmol) as described for **14** gave a dark yellow oil. Purification of the crude product by column chromatography on silica gel ($CHCl_3$-MeOH, 9:1) yielded **16b** (2.526 g, 51%) as white needles from CH_2Cl_2/hexane: mp 125 - 125.5 °C; R_f = 0.32 ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 6.83 (s, 1 H), 6.72 (s, 1 H), 5.39 (br s, 1 H), 4.31 (t, 2 H, J = 7.0 Hz), 3.53 (s, 3 H), 2.93 (t, 2 H, J = 7.0 Hz), 2.69 (d, 3 H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 156.93, 144.70, 127.09, 120.61, 62.32, 32.46, 27.19, 26.77. Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.93. Found: C, 52.47; H, 7.17; N, 23.01.

1-Methyl-2-[3-(N-methylcarbamyloxy)propyl]-1*H*-imidazole (16c)

1-Methyl-2-(3-hydroxypropyl)-1*H*-imidazole[12] (3.67 g, 26.2 mmol) was carbamylated as described for **14** with methyl isocyanate (7.8 mL, 131 mmol) in the presence of a catalytic amount of $Bu_2Sn(OAc)_2$ in dry CH_2Cl_2 (25 mL) to give **16c** as a dark brown oil (4.68 g, 91%): ^1H NMR ($CDCl_3$) δ 6.92 (s, 1 H), 6.79 (s, 1 H), 4.63 (br s, 1 H), 4.15 (t, 2H, J = 6.2 Hz), 3.57 (s, 3 H), 2.79 (d, 3 H, J = 4.8 Hz), 2.73 (t, 2 H, J = 7.6 Hz), 2.13 (m, 2 H).

1-Methyl-2-phenylthio-5-(3-hydroxypropyl)-1*H*-imidazole (17)

To a cooled (-78 °C) solution of 1-methyl-2-phenylthio-1*H*-imidazole[5] (11.93 g, 62.7 mmol) in dry THF (175 mL) was added slowly a solution of *n*-BuLi in hexane (27.6 mL, 69.0 mmol). After being stirred at -78 °C for 45 min, the orange solution was added via canula to a precooled (-78 °C) solution of ethylene oxide (4.50 g, 77.5 mmol) and BF_3-Et_2O (19.3 mL, 157 mmol) in dry THF (75 mL). The mixture was stitrred at -78 °C for an additional 30 min then was warmed gradually to room temperature overnight. The reaction mixture was cooled in ice, quenched with cold aqueous 10% HCl solution (125 mL), saturated with NaCl and extracted with Et_2O (2 x 75 mL). The aqueous layer was basified to pH=10 using 20% NaOH solution and was extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. Removal of the solvent to dryness gave a brown oil, which was purified by column chromatography on silica gel ($CHCl_3$-MeOH, 9:1) to afford **17** as a thick oil (6.35 g, 41%): R_f = 0.35 ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 7.01-7.28 (m, 5 H), 6.93 (s, 1 H), 3.71 (t, 2 H, J = 6.2 Hz), 3.49 (s, 3 H), 3.26 (br s, 1 H), 2.65 (t, 2 H, J = 7.9 Hz), 1.89 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 129.16, 127.48, 127.00, 126.33, 61.17, 31.02, 30.63, 21.48.

1-Methyl-2-phenylthio-5-[3-(N,N-dimethylcarbamoyloxy)propyl]-1*H*-imidazole. (18)

To a cooled (-78 °C) solution of **17** (1.66 g, 6.71 mmol) in dry THF (40 mL) was added dropwise a solution of *n*-BuLi in hexane (2.95 mL, 7.4 mmol). The mixture was stirred at -78 °C for 30 min. Then a solution of N,N-dimethylcarbamoyl chloride (0.82 mL, 8.7 mmol) in THF (10 mL) was added slowly. After 15 min the reaction mixture was allowed to warm to room temperature and was heated to gentle reflux for 30 min. The mixture was cooled to room temperature, carefully basified to pH=10 using aqueous 20% NaOH solution, saturated with NaCl and extracted with $CHCl_3$ (5 x 30 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and filtered. The brown filtrate was evaporated to dryness to give a brown oil. Purification of the crude product by column chromatography on silica gel ($CHCl_3$-MeOH, 9:1) afforded **18** (1.12 g, 52%) as an oil: R_f = 0.6 ($CHCl_3$-MeOH); ^1H NMR ($CDCl_3$) δ 7.11-7.27 (m, 5 H), 6.98 (s, 1 H), 4.16 (t, 2 H, J = 6.3 Hz), 3.52 (s, 3 H), 2.97 (br s, 6 H), 2.64 (t, 2 H, J = 7.7 Hz), 1.96-2.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 156.00, 136.52, 134.91, 134.51, 128.78, 127.20, 126.99, 125.95, 63.88, 38.16, 35.97, 35.45, 30.66, 27.04, 21.43.

1-Methyl-4-[3-(N,N-dimethylcarbamoyloxy)propyl]-1*H*-imidazole (19)

Desulfurization of **18** (0.46 g, 1.45 mmol) with Raney Nickel (ca. 1.7 g) in absolute ethanol as described earlier[12] gave **19** (0.1 g, 34%) as a pale yellow oil: R_f = 0.2 ($CDCl_3$-MeOH); ^1H NMR ($CDCl_3$) δ 7.37 (s, 1 H), 6.79 (s, 1 H), 4.15 (t, 2 H, J = 6.3 Hz), 3.56 (s, 3 H), 2.91 (s, 6 H), 2.62 (t, 2 H, J = 7.6 Hz), 1.93-2.02 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 156.19, 137.28, 130.82, 125.90, 64.08, 36.07, 35.55, 30.85, 27.59, 20.22.

3-(N-Methylcarbamoyloxy)pyridine (20)

3-Hydroxypyridine (4.75 g, 50 mmol) was carbamoylated as described for **14** with methyl isocyanate (6 mL, 0.1 mol) in the presence of a catalytic amount of $Bu_2Sn(OAc)_2$ in dry THF (40 mL). Column chromatography of the crude product on silica gel ($CHCl_3$-MeOH, 9:1) gave **20** (5.47 g, 72%) as a colorless oil: R_f = 0.42 ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 8.41-8.45 (ca, 1 H), 7.51-7.55 (m, 1 H), 7.27-7.32 (m, 1 H), 6.13 (br s, 1 H), 2.83 (d, 3 H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 154.47, 147.70, 145.77, 143.13, 129.07, 123.57, 27.40.

1-Methyl-3-(N-methylcarbamoyloxy)pyridinium Iodide (21)

A mixture of **20** (2.43 g, 16 mmol) and methyl iodide (2 mL, 32 mmol) in dry THF (30 mL) was stirred at room temperature for 16 h and then evaporated to dryness to give a yellow oil. Crystallization of the crude product gave **21** (3.28 g, 66%) as a yellow solid from MeOH/ether: ^1H NMR (D_2O) δ 8.84 (s, 1 H), 8.67 (d, 1 H, J = 6.2 Hz), 8.37 (d, 1 H, J = 8.6 Hz), 8.01 (dd, 1 H, J = 6.2, 8.6 Hz), 4.40 (s, 3 H), 2.83 (s, 3 H).

1-Methyl-1,2,5,6-tetrahydro-3-(N-methylcarbamoyloxy)pyridine (22)

To an ice-cooled solution of **21** (1.84 g, 6.25 mmol) in methanol (10 mL) was added $NaBH_4$ (0.97 g, 25 mmol) in small portions. The mixture was stirred at 0 °C for 30 min, then at room temperature for 1 h. The organic solvent was evaporated under vacuum and the white residue was dissolved in H_2O. The aqueous mixture was extracted with CH_2Cl_2 (6 x 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness to give a brown oil. Purification of the crude product by column chromatography on silica gel ($CHCl_3$-MeOH, 9:1) gave **22** (0.74 g, 70%) as white crystals from acetone/hexane: mp 86.5-87.5 °C; R_f = 0.27 ($CDCl_3$-MeOH, 9:1); IR (KBr)ν_{max} 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.46 (br s, 1 H), 4.80 (br s, 1H), 3.01 (br s, 2 H), 2.82 (d, 3 H, J = 4.8 Hz), 2.53 (t, 2 H, J = 5.7 Hz), 2.38 (s, 3 H), 2.24 - 2.28 (m, 2 H). Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.36; H, 8.27; N, 16.39.

2-Methyl-8-hydroxyimidazo[1,2-a]pyridine (23b)

A mixture of 2-amino-3-hydroxypyridine (1.10 g, 10 mmol) and 2-chloroacetone (0.8 mL, 10 mmol) in dry THF (30 mL) was gently refluxed for 5 h. Then another 0.8 mL of 2-chloroacetone was added and the reaction mixture was stirred at reflux temperature overnight. Solvent was then evaporated to dryness and the resulting residue was quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was filtered to yield **23b** (0.52 g, 35%) as a tan solid. The aqueous filtrate was extracted with $CHCl_3$ (4 x 10 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of solvent gave another 0.26 g (18%) of **23b**: ^1H NMR (D_2O) δ 7.96 (dd, 1 H, J = 1.2, 6.3 Hz); 7.61 (d, 1 H, J = 0.9 Hz), 7.06 (dd, 1 H, J = 6.3, 7.8 Hz), 7.01 (dd, 1 H, J = 1.2, 7.8 Hz), 2.38 (d, 3 H, J = 0.9 Hz); ^{13}C NMR (DMSO-d6) δ 142.60, 133.31, 132.90, 119.29, 117.35, 112.81, 112.43, 10.21.

8-Hydroxy-2-(2-propyl)imidazo[1,2-a]pyridine (23c)

To a hot solution of 2-amino-3-hydroxypyridine (3.3 g, 30 mmol) in absolute ethanol (30 mL) and THF (30 mL) was added dropwise a solution of 1-bromo-3-methylbutan-2-one[7] (4.95 g, 30 mmol). The reaction mixture was gently refluxed overnight and solvent was removed under reduced pressure. The residue was dissolved in methanol and a few drops of concd HBr were added. The mixture was heated on a steam bath for 1 h. Removal of solvent to dryness gave a brown solid, which was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with $CHCl_3$ (6 x 30 mL). The organic layers were washed with H_2O (30 mL), brine (2 x 30 mL) and dried (Na_2SO_4). Evaporation of solvent gave a crude product. Purification of the crude by column chromatography on silica gel ($CHCl_3$-MeOH, 19:1) afforded **23c** (3.9 g, 74%) as white solid from MeOH/Et_2O: mp 162-163°C; R_f = 0.35 ($CHCl_3$-MeOH, 19:1); ^1H NMR ($CDCl_3$) δ 7.6 (dd, 1 H, J = 4.5 Hz), 7.23 (d, 1 H, J = 0.6 Hz), 6.66-6.71 (m, 2 H), 3.09-3.22 (m, 1 H), 1.28 (d, 6 H, J = 6.9 Hz), 0.47 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 151.06, 146.98, 140.18, 116.54, 113.99, 108.28, 108.07, 27.62, 22.39. Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.11; H, 6.90; N, 15.83.

8-Hydroxy-2-phenylimidazo[1,2-a]pyridine (23d)

A mixture of 2-amino-3-hydroxypyridine (1.10 g, 10 mmol) and 2-bromoacetophenone (1.99 g, 10 mmol) in acetone (30 mL) was stirred at 60°C overnight. The volume of solvent was reduced and the mixture was cooled in an ice bath. The resulting solid was filtered, then dissolved in methanol, followed by addition of a few drops of concd HBr solution. The mixture was heated on a steam bath for 1 h. Solvent was evaporated to dryness. The residue was quenched with saturated $NaHCO_3$ solution. The aqueous mixture was extracted with $CHCl_3$ (6 x 20 mL). The organic layers were washed with brine (2 x 20 mL) and dried (Na_2SO_4). Removal of solvent gave **23d** (1.38 g, 66%) as a solid: R_f = 0.56 ($CHCl_3$-MeOH, 9:1); ^{1}H NMR (DMSO-d_6) δ 8.75 (s, 1 H), 8.35 (d, 1 H, J = 6.6 Hz), 8.00 (d, 2 H, J = 7.6 Hz), 7.51-7.60 (m, 3 H), 7.28 (dd, 1 H, J = 6.6, 7.5 Hz), 7.16 (d, 1 H, J = 7.8 Hz).

General Procedure for Carbamoylation of 8-Hydroxyimidazo[1,2-a]pyridine Derivatives

A mixture of 8-hydroxyimidazo[1,2-a]pyridine derivative (1 equiv) and N,N-dimethylcarbamoyl chloride (1.5 equiv) in pyridine was stirred at 80°C for 16 h. Solvent was evaporated under reduced pressure to dryness and the resulting residue was neutralized with saturated $NaHCO_3$ solution. The aqueous mixture was extracted with $CHCl_3$ (6x). The organic layers were washed with water, brine and dried (Na_2SO_4). Removal of solvent gave a crude product.

8-(N,N-Dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (24a)

Following the general procedure for carbamoylation, the reaction of 8-hydroxyimidazo[1,2-a]pyridine[13] **23a** (8.5 g, 5.0 mmol) with N,N-dimethylcarbamoyl chloride (0.69 mL, 7.5 mmol) in pyridine (5 mL) gave **24a** (0.67 g, 65%) as a white solid after purification by column chromatography (silica gel; $CHCl_3$-MeOH, 25:1) followed by recrystallization in EtOAc/hexane: mp 128-129.5 °C; R_f = 0.29 ($CHCl_3$-MeOH, 25:1); ^{1}H NMR ($CDCl_3$) δ 7.86 (br d, 1 H , J = 6.9 Hz), 7.48 (br d, 2H, J = 8.7 Hz), 6.86 (br d, 1 H, J = 7.4 Hz), 6.57 (dd, 1 H, J = 6.9, 7.4 Hz), 3.12 (s, 3 H), 2.94 (s, 3 H). ^{13}C NMR ($CDCl_3$)δ 153.70, 140.95, 140.72, 133.46, 123.06, 115.35, 113.19, 111.42, 36.80, 36.67. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40 N, 20.48. Found: C, 58.46 H, 5.46; N, 20.53.

2-Methyl-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (24b)

Following the general procedure for carbamoylation of 8-hydroxyimidazo[1,2-a]-pyridine derivatives, **23b** (0.74 g, 5 mmol) and N,N-dimethylcarbamoyl chloride in dry pyridine yielded **24b** (0.8 g, 74%) as an off-white solid from EtOAc/hexane: mp 80.5-81.5 °C; R_f = 0.41 ($CHCl_3$-MeOH, 19:1); ^1H NMR ($CDCl_3$) δ 7.88 (dd, 1 H, J = 0.9, 6.8 Hz), 7.35 (s, 1 H), 6.92 (dd, 1 H, J = 0.9, 7.5 Hz), 6.67 (dd, 1 H, J = 6.8, 7.5 Hz), 3.21 (s, 3 H), 3.03 (s, 3 H), 2.46 (d, 3 H, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 153.91, 143.46, 140.60, 139.87, 122.46, 115.20, 110.84, 110.52, 36.83, 36.78, 14.50. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.19; H, 6.01; N, 19.21.

8-(N,N-Dimethylcarbamoyloxy)-2-(2-propyl)imidazo[1,2-a]pyridine (24c)

Following the general procedure for carbamoylation of 8-hydroxyimidazo-[1,2-a]pyridine derivatives, the reaction of **23c** (2.7 g, 15.3 mmol) with N,N-dimethyl-carbamoyl chloride (2.1 mL, 23.0 mmol) in pyridine (30 mL) gave a crude product, which was purified by column chromatography (silica gel; EtOAc-hexane, 4:1) to give **24c** (2.71 g, 71 %) as a white solid from EtOAc/hexane: mp 100-101°C; R_f = 0.33 (EtOAc-hexane, 4:1); ^1H NMR ($CDCl_3$) δ 7.90 (dd, 1 H, J = 0.9, 6.9 Hz), 7.35 (s, 1 H), 6.91 (dd, 1 H, J = 0.9, 7.5 Hz), 6.65 (dd, 1 H, J = 6.9, 7.5 Hz), 3.22 (s, 3 H), 3.08-3.20 (m, 1 H), 3.02 (s, 3 H), 1.34 (d, 6 H, J = 6.9 Hz). Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.01; H, 6.92; N, 16.98.

8-(N,N-Dimethylcarbamoyloxy)-2-phenylimidazo[1,2-a] pyridine (24d)

Following the general procedure for carbamoylation of 8-hydroxyimidazo[1,2-a]-pyridine derivatives, treatment of **23d** (1.1 g, 5.2 mmol) with N,N-dimethylcarbamoyl chloride (0.72 mL, 7.8 mmol) in pyridine (10 mL) gave a crude product. Purification of the crude by column chromatography (silica gel; $CHCl_3$-MeOH, 20:1) afforded **24d** (1.2 g, 82%) as an off-white solid: mp 132-132.5°C; R_f = 0.58 ($CHCl_3$-MeOH, 20:1); ^1H NMR ($CDCl_3$) δ 7.93 (dd, 1 H, J = 1.5, 8.7 Hz), 7.89 (dd, 1 H, J = 1.0, 6.8 Hz), 7.81 (s, 1 H), 7.37-7.41 (m, 2 H), 7.25-7.32 (m, 1 H), 6.96 (dd, 1 H, J = 1.0, 7.5 Hz), 6.63 (dd, 1 H, J = 6.8, 7.5 Hz), 3.24 (s, 3 H), 3.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.88, 145.66, 141.03, 140.41, 133.63, 128.42, 127.74, 126.16, 122.78, 115.48, 111.38, 109.06, 36.77. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.41; H, 5.44; N, 14.92.

5-Aminoimidazo[1,2-a]pyridine Hydrochloride (25a)

A mixture of 2,6-diaminopyridine (10.9 g, 0.1 mol) and chloroacetaldehyde (17.5 g, 45% w/w in water, 0.1 mol) in acetone (200 mL) was refluxed overnight. The reaction mixture was cooled and filtered to give a solid, which was washed with several portions of fresh acetone and dried under vacuum to afford **25a** (16.9 g, 100%) as tan solid: ^1H NMR (DMSO-d_6) δ 8.45 (d, 1 H, J = 2.4 Hz), 8.08 (d, 1 H, J = 2.4 Hz), 7.99 (br s, 2 H), 7.69 (dd, 1 H, J = 7.8, 8.4 Hz), 7.00 (d, 1 H, J = 8.4 Hz), 6.49 (d, 1 H, J = 7.8 Hz).

2-Methyl-5-aminoimidazo[1,2-a]pyridine (25b)

To a mixture of 2,6-diaminopyridine (10.9 g, 0.1 mol) in absolute ethanol (100 mL) at 70 °C was added dropwise a solution of chloroacetone (7.96 mL, 0.1 mol) in absolute ethanol (30 mL). The mixture was gently refluxed overnight. Additional chloroacetone (2 mL) was added and the mixture was refluxed for 5 h. The solvent was reduced to 1/3 of its original volume and Et_2O was added. The mixture was cooled in an ice bath to give a solid which was dissolved in water and neutralized with a saturated $NaHCO_3$ solution. The volume of water was reduced to give **25b** (7.2 g, 48.6%) as black solid: mp 155-156.5 °C; R_f = 0.17 ($CHCl_3$-MeOH, 9:1); ^1H NMR (DMSO-d_6) δ 7.52 (s, 1 H), 7.02 (dd, 1 H, J = 7.4, 8.7 Hz), 6.68 (d, 1 H, J = 8.7 Hz), 6.45 (br s, 2 H), 5.89 (dd, 1 H, J = 0.8, 7.4 Hz), 2.29 (d, 3 H, J = 0.8 Hz); ^{13}C NMR (DMSO-d_6) δ. 145.79, 142.00, 141.29, 126.33, 104.22, 102.13, 89.48, 14.39. Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.02; H, 6.15; N, 28.28.

2-Phenyl-5-aminoimidazo[1,2-a]pyridine (25d)

A solution of 2-bromoacetophenone (19.9 g, 0.1 mol) in dry THF (60 mL) was added dropwise to a mixture of 2,6-diaminopyridine (10.9 g, 0.1 mol) in THF (80 mL) at reflux temperature. The mixture was stirred at reflux overnight. 2,6-Diaminopyridine (3g) was added to the mixture which was refluxed for a further 5 h. The solvent was evaporated to dryness and the resulting residue was washed with Et_2O (3 x 100 mL) and then dissolved in methanol (150 mL). Concentrated HBr solution (3 mL) was added and the mixture was stirred at reflux for 30 min. Solvent was evaporated to dryness. The residue was neutralized with saturated aqueous $NaHCO_3$ solution and the mixture was extracted with $CHCl_3$ (4 x 100 mL). The organic layers were washed with brine, dried (Na_2SO_4) and filtered via a column of silica gel, eluted with a mixture of 20% hexane in ethyl acetate to give **25d** (5.27 g, 25.2%): R_f = 0.44 (EtOAc-hexane, 4:1); ^1H NMR ($CDCl_3$) δ 7.94, (dd, 2 H, J = 1.4, 8.4 Hz), 7.64 (s, 1 H), 7.37 - 7.43 (m, 2 H), 7.29-7.34 (m, 1 H), 7.17 (d, 1 H, J = 8.8 Hz), 7.09 (dd, 1 H, J = 7.2, 8.8 Hz), 6.04 (dd, 1 H, J = 1.1, 7.2 Hz), 4.45 (br s, 2 H).

General Procedure for Preparation of 5-Hydroxyimidazo[1,2-a]pyridine Derivatives[14]

A mixture of 2-substituted-5-aminoimidazo[1,2-a]pyridine in an aqueous 70% H_2SO_4 solution was stirred at 120 °C (oil bath temperature) for 10 h. The mixture was cooled and carefully neutralized with an aqueous 20% NaOH solution. Filtration of the mixture gave the product, which was washed with several portions of water and dried under vacuum.

5-Hydroxyimidazo[1,2-a]pyridine (26a)

Following the general procedure for preparation of 5-hydroxyimidazo-[1,2-a]pyridine derivatives, **25a** (16.6 g, 97.8 mmol) afforded **26a** (10.93g, 75.4%) as an olive green solid: R_f = 0.53 ($CHCl_3$-MeOH, 9:1); ^1H NMR (DMSO-d_6) δ 7.64 (d, 1 H, J = 2.1 Hz), 7.53 (d, 1 H, J = 2.1 Hz), 7.34 (dd, 1 H, J = 8.1, 8.4 Hz), 6.15 (d, 1 H, J = 8.1 Hz), 5.63 (d, 1 H, J = 8.4 Hz), 1.82 (br s, 1 H).

2-Methyl-5-hydroxyimidazo[1,2-a]pyridine (26b)

Following the general procedure for preparation of 5-hydroxyimidazo [1,2-a]pyridine derivatives, **25b** (3.4 g, 23.1 mmol) gave **26b** (2.64 g, 77.2%): R_f = 0.39 ($CHCl_3$-MeOH, 9:1); ^1H NMR (DMSO-d_6) δ 7.38 (s, 1 H), 7.28 (dd, 1 H, J = 7.8, 8.4 Hz), 6.08 (d, 1 H, J = 7.8 Hz), 5.60 (d, 1 H, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ 155.55, 142.21, 135.89, 127.85, 105.04, 97.00, 84.52, 10.25.

2-Phenyl-5-hydroxyimidazo[1,2-a]pyridine (26d)

Following the general procedure for preparation of 5-hydroxyimidazo-[1,2-a]pyridine derivatives, **25d** (2.83 g, 13.5 mmol) gave **26d** (2.62 g, 92.2 %) as an olive green solid: R_f = 0.68 ($CHCl_3$-MeOH, 9:1); ^1H NMR (DMSO-d_6) δ 8.24 (s, 1 H), 7.89 (d, 2 H, J = 7.8 Hz), 7.35 - 7.50 (m, 5 H), 6.24 (d, 1 H, J = 8.1 Hz), 5.72 (d, 1 H, J = 8.4 Hz).

General Procedure for Carbamoylation of 5-Hydroxyimidazo[1,2-a]pyridine Derivatives

A mixture of 5-hydroxyimidazo[1,2-a]pryridine derivative (1equiv) and sodium hydride (1.5 equiv) in dry DMF was stirred at room temperature for 30 min, then at 50 °C for 30 min. N,N-Dimethylcarbamoyl chloride (1.5 equiv) was added slowly by syringe and the reaction mixture was stirred at 80 °C for 10 h. Solvent was evaporated under vacuum. The resulting residue was partitioned between an aqueous $NaHCO_3$ solution and $CHCl_3$. Insoluble material was removed by filtration. The aqueous phase was extracted with $CHCl_3$. The organic layers were washed with brine, dried (Na_2SO_4) and filtered. Removal of solvent gave a crude product which was purified by column chromatography.

2 -Methyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (27b)

Following the general procedure for carbamoylation of 5-hydroxyimidazo[1,2-a]-pyridine, **26b** (1.1. g, 7.4 mmol). gave a crude product which was purified by column chromatography (silica gel; gradient elution, 4 to 8% of MeOH in $CHCl_3$) to give **27b** (1.09 g, 67.3%) as an off-white solid from EtOAc/hexane: mp 110 - 111 °C; R_f = 0.59 ($CHCl_3$-MeOH, 24:1); ^1H NMR ($CDCl_3$) δ 7.38 (d, 1 H, J = 8.7 Hz), 7.27 (s, 1 H), 7.16 (dd, 1 H, J = 7.5, 8.7 Hz), 6.59 (d, 1 H, J = 7.5 Hz), 3.20 (s, 3 H), 3.06 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.58, 146.43, 143.31, 140.14, 112.92, 104.83, 101.29, 36.90, 36.52, 14.27. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.25; H, 5.99; N, 19.06.

2-Phenyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (27d)

Following the general procedure for carbamoylation of 5-hydroxyimidazo[1,2-a]-pyridine, **26d** (2.6 g, 12.3 mmol) afforded a crude product which was purified by column chromatography (silica gel; 2% of MeOH in $CHCl_3$) to give **27d** (1 g, 29%) as a yellow solid from EtOAc/hexane: mp 152-153 °C; R_f = 0.57 ($CHCl_3$-MeOH, 24:1); ^1H NMR ($CDCl_3$) δ 7.98 (d, 2 H, J = 7.2 Hz), 7.78 (s, 1 H), 7.51 (d, 1 H, J = 9.0 Hz), 7.43 (dd, 2 H, J = 7.2, 7.8 Hz), 7.32 (m, 1 H), 7.22 (dd, 1 H, J = 7.5, 9.0 Hz), 6.65 (d, 1 H, J = 7.5

Hz), 3.24 (s, 3 H), 3.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.68, 147.18, 145.85, 140.66, 133.63, 128.60, 128.00, 126.19, 125.17, 113.80, 103.55, 101.97, 37.16, 36.78. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.24; H, 5.40; N, 14.89.

1-Methylimidazo[1,2-a]pyridin-5-one (28)

A mixture of **26a** (2.68 g, 20 mmol) and $NaNH_2$ (1.09 g, 28 mmol) in dry DMF (30 mL) was stirred at room temperature for 30 min. Methyl iodide (1.62 mL, 26 mmol) was added dropwise by syringe and the mixture was stirred at room temperature for 2 h. Solvent was evaporated to dryness under vacuum and the resulting residue was partitioned between an aqueous $NaHCO_3$ solution and $CHCl_3$. Insoluble material was removed by filtration. The aqueous layer was extracted with $CHCl_3$ (5 x 50 mL). The organic layers were washed with brine (2 x 50 mL), dried (Na_2SO_4) and filtered. Removal of solvent yielded a crude product which was purified by column chromatography (silica gel, 5% of MeOH in $CHCl_3$) to afford **28** (1.44 g, 48.6 %) as an off-white solid from acetone/hexane: $R_f = 0.38$ ($CHCl_3$-MeOH, 19:1); ^1H NMR ($CDCl_3$) δ 7.74 (d, 1 H, J = 2.4 Hz), 7.44 (t, 1 H, J = 8.4 Hz), 6.97 (d, 1 H, J = 2.4 Hz), 6.01 (d, 2 H, J = 8.4 Hz), 3.68 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.97, 142.44, 136.98, 120.24, 108.46, 99.41, 83.47, 32.85.

2-(2-Propyl)-6-hydroxyimidazo[1,2-a]pyridine (29)

A mixture of 2-amino-5-benzoyloxypyridine[15] (0.89 g, 4.2 mmol) and 1-bromo-3-methylbutan-2-one (0.75g, 4.6 mmol) in dry THF (15 mL) was refluxed for 16 h. Solvent was removed to dryness and the resulting residue was treated with aqueous 20% KOH solution. The mixture was stirred at 100 °C (oil bath temperature) for 1 h. The reaction mixture was cooled and neutralized with concentrated HCl solution to give solid **29** (0.52 g, 71 %): $R_f = 0.43$ ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 7.76 (d, 1 H, J = 1.8 Hz), 7.19 (overlapped d, 1 H, J = 9.6 Hz), 7.18 (overlapped s, 1 H), 7.02 (dd, 1 H, J = 1.8, 9.6 Hz), 3.08 (septet, 1 H, J = 7.1 Hz), 1.32 (d, 6 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 151.97, 147.48, 140.81, 121.46, 115.01, 110.72, 107.87, 27.92, 22.46.

2-(2-Propyl)-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (30)

A mixture of **29** (0.21 g, 1.2 mmol) and dimethylcarbamoyl chloride (0.19 g, 1.8 mmol) in dry pyridine (10 mL) was stirred at 80 °C overnight. Solvent was then evaporated to dryness under reduced pressure and the resulting residue was partitioned between aqueous $NaHCO_3$ solution and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (6 x 20 mL). The organic layers were washed with brine (2 x 20 mL), dried (Na_2SO_4), filtered and evaporated to dryness. Purification of the crude by column chromatography (silica gel; EtOAc-hexane, 4:1) afforded **30** (0.21 g, 70%): $R_f = 0.29$ (EtOAc-hexane, 4:1); ^1H NMR ($CDCl_3$) δ 7.95 (d, 1 H, J = 2.2 Hz), 7.39 (d, 1 H, J = 9.9 Hz), 7.20 (s, 1 H), 6.87 (dd, 1 H, J = 2.2, 9.9 Hz), 2.92-3.07 (overlapped m, 4 H), 2.91 (s, 3 H), 1.26 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 154.75, 154.20, 142.90, 139.51, 120.89, 118.06, 116.19, 108.15, 36.50, 36.19, 28.21, 22.20.

General Procedure for Quaternization of Carbamates

A mixture of carbamate (1 equiv) and methyl *p*-toluenesulfonate or methyl iodide (1.5 equiv) in dry THF (or CH_3CN) was stirred at 60 °C overnight. Ether was added and the reaction mixture was cooled in ice. The precipitate was filtered, decolorized and recrystalization to yield the product.

3-Methyl-1-[(N,N-dimethylcarbamyloxy)methyl]-1*H*-imidazolium Iodide (1a) (PN-II-32)

Following the general procedure for quaternization, the reaction of **11a** (2.3 g, 13.6 mmol) with methyl iodide (1.69 mL, 27 mmol) in dry THF (10 mL) gave a crude white solid **1a** (4.16 g, 98%) which was recrystallized in MeOH/Et_2O: mp 171-172 °C; IR (KBr)$_{vmax}$ 3155, 3102, 1701, 1180, 1147, 1054 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9,32 (s, 1 H), 7.85 (s, 1 H), 7.73 (s, 1 H), 6.05 (s, 2 H), 3.88 (s, 3 H), 2.86 (s, 3 H), 2.83 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 153.86, 137.97, 123.75, 122.44, 36.19, 36.05, 35.60. Anal. Calcd for $C_8H_{14}IN_3O_2$: C, 30.88; H, 4.53; N, 13.50. Found: C, 30.94; H, 4.57; N, 13.50.

3-Methyl-1-[2-(N,N-dimethylcarbamyloxy)ethyl]-1*H*-imidazolium Iodide (1b) (PN-II-112)

Following the general procedure for quaternization, the reaction of **11b** (1.83 g, 10 mmol) with methyl iodide (2.5 mL, 40 mmol) in dry THF (10 mL) yielded **1b** (2.85 g, 87%) as a white solid from acetone/ether: mp 87-88 °C; IR (KBr)$_{vmax}$ 3146, 3084, 1701, 1192 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.15 (s, 1 H), 7.77 (brs, 1 H), 7.72 (br s, 1 H), 4.45 (t, 2 H, J = 4.8 Hz), 4.29 (t, 2 H, J = 4.8 Hz), 3.86 (s, 3 H), 2.78 (s, 6 H); ^{13}C NMR (DMSO-

d_6) δ 154.89, 136.86, 123.59, 122.71, 63.03, 48.39, 36.08, 35.89, 35.56. Anal. Calcd for $C_9H_{16}IN_3O_2$: C, 33.24; H, 4.96; N, 12.92. Found: C, 33.32; H, 4.99; N, 12.87.

3-Methyl-1-[3-(N,N-dimethylcarbamyloxy)propyl]-1*H*-imidazolium Iodide (1c) (PN-II-108)

Following the general procedure for quaternization, the reaction of **11c** (0.513 g, 2.5 mmol) with methyl iodide (0.32 mL, 5.2 mmol) in THF (5 mL) yielded a thick, pale yellow oil which gave a white solid **1c** (0.85 g, 96%) on standing in the freezer. Analytical sample was recrystallized from acetone: mp 117.5-118 °C; IR (KBr)ν_{max} 3142, 3067, 1703, 1197 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.13 (s, 1 H), 7.78 (d, 1 H, J = 1.5 Hz), 7.71 (d, 1 H, J = 1.5 Hz), 4.24 (t, 2 H, J = 7.1 JHz), 4.00 (t, 2 H, J = 6.0 Hz), 3.84 (s, 3 H), 2.79 (s, 6 H), 2.07-2.16 (m, 2 H). Anal. Calcd for $C_{10}H_{18}IN_3O_2$: C, 35.39; H, 5.35; N, 12.39. Found: C, 35.46; H, 5.37; N, 12.33.

3-Methyl-1-[2-(N-methylcarbamoyloxy)ethyl]-1*H*-imidazolium Iodide (2b) (PN-II-184)

Following the general procedure for quaternization, the reaction of **14** (1.44 g, 8.5 mmol) and methyl iodide (1.64 mL, 25.5 mmol) in THF (10 mL) and CH_3CN (4 mL) at room temperature gave **2b** (2.15 g, 81%) as white needles from acetone/ether: mp 104-105 °C; IR (KBr)ν_{max} 3248, 3145, 3115, 1710 cm^{-1}; ^1H NMR (DMSO-d_6 + $CDCl_3$) δ 9.63 (s, 1 H), 7.79 (s, 1 H), 7.61 (s, 1 H), 6.70 (br s, 1 H), 4.59 (dd, 2 H, J = 4.5, 5.1 Hz), 4.37 (dd, 2 H, J = 4.5, 5.1 Hz), 4.10 (s, 3 H), 2.70 (d, 3 H, J = 8.1 Hz); ^{13}C NMR (DMSO-d_6 + $CDCl_3$) δ 155.11, 136.26, 122.56, 122.30, 61.09, 48.42, 35.89, 26.15. Anal. Calcd for $C_8H_{14}IN_3O_2$: C,30.88; H, 4.54; N, 13.51. Found: C, 30.95; H, 4.55; N, 13.52.

3-Methyl-1-[3-(N-methylcarbamoyloxy)propyl]-1*H*-imidazolium Iodide (2c) (PN-II-178)

Following the general procedure for quaternization, the reaction of **15** (1.83 g, 10 mmol) with methyl iodide in dry THF (15 mL) gave **2c** (2.86 g, 88%) as white needles from acetone/ether: mp 82-82.5 °C; IR (KBr)ν_{max} 3076, 1709 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.11 (s, 1 H), 7.76 (s, 1 H), 7.70 (s, 1 H), 6.91 (br s, 1 H), 4.21 (t, 2 H, J = 6.4 Hz), 3.95 (t, 2 H, J = 6.1 Hz), 3.84 (s, 3 H), 2.54 (d, 3 H, J = 4.8 Hz), 2.05-2.12 (m, 2 H); ^{13}C NMR

(DMSO-d_6) δ 156.45, 136.64, 123.60, 122.26, 60.54, 46.16, 35.81, 29.08, 26.91. Anal. Calcd for $C_9H_{16}IN_3O_2$: C, 33.25; H, 4.96; N, 12.92. Found: C, 33.25; H, 4.94; N, 12.87.

1,3-Dimethyl-2-[2-(N-methylcarbamyloxy)ethyl]-1*H*-imidazolium Iodide (4b) (PN-II-68)

Following the general procedure for quaternization, the reaction of **16b** (0.46 g, 2.5 mmol) with methyl iodide (0.3 mL, 5 mmol) gave a white solid **4b** (0.76 g, 93%): mp 142-143 °C from MeOH/Et_2O; IR (KBr)$_{\nu max}$ 3315, 3117, 3090, 1724 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.65 (s, 2 H), 7.06 (br m, 1 H). 4.19 (t, 2 H, J = 5.9 Hz), 3.79 (s, 6 H), 3.34 (t, 2 H, J = 5.9 Hz), 2.46 (d, 3 H, J = 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 155.84, 144.24, 122.59, 59.92, 35.03, 26.79, 23.29. Anal. Calcd for $C_9H_{16}IN_3O_2$: C, 33.25; H, 4.96; N, 12.92. Found: C, 33.33; H, 4.96; N, 12.98.

1,3-Dimethyl-2-[3-(N-methylcarbamyloxy)propyl]-1*H*-imidazolium Iodide (4c) (PN-II-62)

Following the general procedure for quaternization, the reaction of **16c** (4.15 g, 21 mmol) with methyl iodide (2.6 mL, 42 mmol) in THF (20 mL) gave **4c** (6.6 g, 92%), as white needles from MeOH/Et_2O: mp 146-147 °C; IR (KBr)$_{\nu max}$ 3289, 3115, 3088, 1723, 1248, 1141 cm^{-1}; ^1H NMR (DMSO) δ 7.60 (s, 2 H), 6.89 (br m, 1 H), 3.93 (t, 2 H, J = 6.0 Hz), 3.76 (s, 6 H), 3.03 (t, 2 H, J = 7.6 Hz), 2.50 (d, 3 H, J = 4.5 Hz), 1.83-1.90 (m, 2 H); ^{13}C NMR (DMSO) δ 156.38, 146.16, 122.33, 62.34, 34.82, 26.82, 25.19, 19.38. Anal. Calcd for $C_{10}H_{18}IN_3O_2$: C, 35.41; H, 5.35; N, 12.39. Found: C, 35.25; H, 5.42; N, 12.32.

1,3-Dimethyl-5-[3-(N,N-dimethylcarbamyloxy)propyl]-1*H*-imidazolium Iodide (5c) (PN-I-292)

Following the general procedure for quaternization, the reaction of **19** (95 mg, 0.45 mmol) with methyl iodide (0.14 mL, 2.25 mmol) gave **5c** (134 mg, 85%), white needles from acetone/Et_2O: mp 115-116 °C; IR (KBr)$_{\nu max}$ 3012, 1701, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.00 (s, 1 H), 7.22 (s, 1 H), 4.18 (t, 2 H, J = 6.2 Hz), 1.99-2.09 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.30, 135.06, 119.86, 63.28, 36.83, 36.45, 36.01, 34.21, 28.82, 20.23. Anal. Calcd for $C_{11}H_{20}IN_3O_2$: C, 37.40; H, 5.70; N, 11.89. Found: C, 37.45; H, 5.74; N, 11.81.

1,1-Dimethyl-1,2,5,6-tetrahydro-3-(N-methylcarbamoyloxy)pyridinium Iodide (6) (PN-II-198)

Following the general procedure for quaternization, the reaction of **22** (0.45 g, 2.64 mmol) with methyl iodide (0.5 mL, 7.9 mmol) in dry THF (4 mL) gave **6** (0.75 g, 91%) as a white solid from CH_3CN/ether: mp 172-173 °C; IR (KBr)$_{vmax}$ 1730, 1709 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.59 (br m, 1 H), 5.67 (br s, 1 H), 4.00 (br s, 2 H), 3.45 (t, 2 H, J = 6.2 Hz), 3.12 (s, 6 H), 2.59 (d, 3 H, J = 4.5 Hz), 2.46 - 2.54 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 153.88, 138.76, 110.25, 59.49, 57.27, 50.79, 26.93, 19.23. Anal. Calcd for $C_9H_{17}IN_2O_2$: C, 34.63; H, 5.50; N, 8.97. Found: C, 34.72; H, 5.51; N, 9.02.

1-Methyl-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium *p*-Toluenesulfonate (10a) (PN-II-278)

Following the general procedure for quaternization, the reaction of **24a** (0.96 g, 4.68 mmol) with methyl *p*-toluensulfonate (1.3 g, 7.0 mmol) in THF (20 mL) gave **10a** (1.38 g, 75%) as white solid from CH_3CN/Et_2O: mp 145-145.5°C; IR (KBr)$_{vmax}$ 3107, 3086, 1751, 1199 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.12 (d, 1 H, J = 6.8 Hz), 8.79 (d, 1 H, J = 2.1 Hz), 8.33 (d, 1 H, J = 2.1 Hz), 7.78 (d, 2 H, J = 8.0 Hz), 7.51 (d, 1 H, J = 7.8 Hz), 7.25 (dd, 1 H, J = 6.8, 7.8 Hz), 7.12 (d, 2 H, J = 8.0 Hz), 4.20 (s, 3 H), 3.15 (s, 3 H), 3.04 (s, 3 H), 2.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 152.72, 144.07, 139.13, 136.66, 134.17, 128.61, 128.49, 128.11, 125.86, 116.85, 116.42, 37.34, 36.79, 36.66, 21.27. Anal. Calcd for $C_{18}H_{21}N_3O_5S$: C, 55.23; H, 5.41; N, 10.73. Found: C, 55.29; H, 5.40; N, 10.72.

1,2-Dimethyl-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Tosylate (10b) (PN-II-222)

Following the general procedure for quaternization, the reaction of **24b** (0.4 g, 1.82 mmol) and methyl *p*-toluenesulfonate (0.5 g, 2.7 mmol) in THF (5 mL) afforded **10b** (0.52 g, 70%) as an off-white solid from methanol/ether: mp 205-207 °C; IR (KBr)$_{vmax}$ 3136, 3049, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.06 (dd, 1 H, J = 0.6, 6.6 Hz), 8.57 (s, 1 H), 7.73 (d, 2 H, J = 8.1 Hz), 7.47 (dd, 1 H, J = 0.6, 7.8 Hz), 7.21 (dd, 1 H, J = 6.6, 7.8 Hz), 7.06 (dd, 2 H, J = 8.1 Hz), 3.99 (s, 3 H), 3.18 (s, 3 H), 3.04 (s, 3 H), 2.44 (s, 3 H), 2.28 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 152.67, 144.23, 138.72, 136.02, 135.62, 134.18, 128.31, 127.42, 125.74, 125.55, 116.43, 114.34, 37.21, 36.78, 32.77, 21.13, 9.92.

Anal. Calcd for: $C_{19}H_{23}N_3O_5S$: C, 56.28; H, 5.72; N, 10.36. Found: C, 56.25; H, 5.73; N, 10.31.

1-Methyl-2-(2-propyl)-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]-pyridinium *p*-Toluenesulfonate (10c) (PN-III-28)

Following the general procedure for quaternization, the reaction of **24c** (1.1 g, 4.45 mmol) with methyl *p*-toluenesulfonate (1.24 g, 6.67 mmol) in CH_3CN (20 mL) gave **10c** (1.72 g, 89 %) as white solid from CH_3CN/Et_2O: mp 125-126°C; IR (KBr)$_{vmax}$ 3099, 3040, 1734, 1720, 1219 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9,19 (d, 1 H, J= 6.7 Hz), 8.63 (s, 1 H), 7.76 (d, 2 H, J = 7.9 Hz), 7.48 (d, 1 H, J = 7.8 Hz), 7.22 (dd, 1 H, J = 6.7, 7.8 Hz), 7.06 (d, 2 H, J = 7.9 Hz), 4.03 (s, 3 H), 3.20 (s, 3 H), 3.08-3.18 (m, 1 H), 3.05 (s, 3 H), 2.28 (s, 3 H), 1.31 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 152.73, 145.16, 144.34, 138.61, 136.02, 134.37, 128.24, 128.06, 125.83, 125.79, 116.44, 113.05, 37.23, 36.00, 32.78, 24.22, 21.17, 21.11. Anal. Calcd for $C_{21}H_{27}N_3O_5S$: C, 58.18; H, 6.28; N, 9.69. Found: C, 57.98; H, 6.33; N, 9.58.

1-Methyl-2-phenyl-8-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (10d) (PN-II-258)

Following the general procedure for quarternization, the reaction of **24d** (2.0g, 7.1 mmol) with methyl iodide (1.32 mL, 21.3 mmol) in THF (25 mL) yielded **10d** (2.47 g, 82%) as white needles from CH_3CN/Et_2O: mp 165-165.5°C; IR (KBr)$_{vmax}$ 3057, 1741, 1143 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.38 (d, 1 H, J = 6.7 Hz), 8.95 (s, 1 H), 7.68 (d, 1 H, J = 7.8 Hz), 7.52-7.62 (m, 5 H), 7.36 (dd, 1 H, J = 6.7, 7.8 Hz), 4.00 (s, 3 H), 3.27 (s, 3 H), 3.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 152.60, 138.73, 136.75, 134.86, 131.05, 130.15, 129.30, 126.92, 126.44, 123.96, 117.07, 113.88, 37.34, 37.19, 34.63. Anal. Calcd for $C_{17}H_{18}IN_3O_2$: C, 48.24; H, 4.29; N, 9.93. Found: C, 48.34; H, 4.25; N, 9.97.

1-Methyl-5-(N.N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Chloride (7a)

To a mixture of **28** (0.29 g, 2 mmol) in dry THF (5 mL) and HMPT (0.7 mL, 4 mmol) was added slowly Me_2NCOCl (0.36 mL, 4 mmol). The rection mixture was stirred at 60 °C overnight, then cooled in an ice bath. Solvent was carefully removed by pipette and the solid was washed with ether and dried. Recrystallization of the crude in MeOH/ether gave **7a** as a grey solid: ^{1}H NMR ($CDCl_3$) δ 9.90 (d, 1 H, J = 2.0 Hz), 8.12

(d, 1 H, J = 2.0 Hz), 8.07 (d, 1 H, J = 9.0 Hz), 8.00 (dd, 1 H, J = 7.7, 9.0 Hz), 7.32 (d, 1 H, J = 7.7 Hz), 4.42 (s, 3 H), 3.29 (s, 3 H), 3.12 (s, 3 H). Anal. Calcd for $C_{11}H_{14}ClN_3O_2.2/3\ H_2O$ C, 49.35; H, 5.77; N,, 25.69. Found: C, 49.55; H, 5.70; N, 15.32.

1,2-Dimethyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium *p*-Toluenesulfonate (7b) (PN-III-190)

Following the general procedure for quaternization, **27b** (1.2 g, 5.5. mmol) was reacted with methyl*p*-toluenesulfonate (1.52 g, 8.2 mmol) in dry THF (10 mL) to give **7b** (2.15 g, 96.8 %) as a white solid from CH_3CN/ether: mp 162-162.5 °C; IR (KBr) ν_{max} 3094, 1755, 1205, 1190, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.98 (d, 1 H, J = 9.0 Hz), 7.84 (dd, 1 H, J = 7.8, 9.0 Hz), 7.68 (d, 2 H, J = 8.3 Hz), 7.19 (d, 1 H, J = 7.8 Hz), 7.03 (d, 2 H, J = 8.3 Hz), 4.00 (s, 3 H), 3.23 (s, 3 H), 3.04 (s, 3 H), 2.54 (s, 3 H), 2.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.23, 144.44, 141.63 140.30, 138.49, 135.99, 134.23, 128.17, 125.79, 108.27, 107.51, 107.11, 37.35, 37.10, 31.67, 21.13, 9.95. Anal. Calcd for $C_{19}H_{23}N_3O_5S$: C, 56.28; H, 5.72; N, 10.36. Found: C, 56.40; H, 5.67; N, 10.44.

1-Methyl-2-phenyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (7d)

Following the general procedure for quaternization, the reaction of **27d** (0.37 g, 1.3 mmol) and methyl iodide (0.78 g, 2.8 mmol) in dry THF yielded **7d** (0.92 g, 78.5%) as white needles from CH_3CN/Et_2O: mp 156-157 °C; ^1H NMR ($CDCl_3$) δ 8.16 (d, 1 H, J = 9.0 Hz), 8.04 (dd, 1 H, J = 8.0; 9.0 Hz), 7.96 (s, 1 H), 7.71-7.75 (m, 2 H), 7.57-7.62 (m, 3 H), 7.36 (dd, 1H, J = 0.6, 8.0 Hz), 4.15 (s, 3 H), 3.29 (s, 3 H), 3.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.22, 142.09, 140.90, 138.93, 135.35, 131.22, 130.29, 129.39, 124.29, 108.77, 108.16, 108.04, 37.59, 34.18.

1-Methyl-2-(2-propyl)-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (8c)

Following the general procedure for quaternization, the reaction of **30** (0.85 g, 3.4 mmol) with methyl iodide gave **8c** (1.28g, 95.8%) as white solid from CH_3CN/Et_2O: mp 180-181 °C; ^1H NMR ($CDCl_3$) δ 9.10 (dd, 1 H, J = 0.9, 2.1 Hz), 8.58 (s, 1 H), 8.28 (d, 1 H, J = 9.9 Hz), 7.77 (dd, 1 H, J = 2.1, 9.9 Hz), 4.15 (s, 3 H), 3.26 (septet, 1 H, J = 6.9 Hz), 3.14 (s, 3 H), 3.02 (s, 3 H), 1.43 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ

153.11, 145.49, 143.40, 137.49, 135.52, 121.77, 112.09, 111.40, 37.10, 36.84, 33.04, 24.96, 21.55

Acetylcholinesterase Inhibition

AChE activity was determined by the spectrophotometric method of Ellman[8] using 0.075 M acetylthiocholine iodide as a specific substrate for AChE. Varying concentrations (10^{-4} to 10^{-8}) of inhibitor were prepared and the concentrations of inhibitor required to inhibit AChE activity *in vitro* by 50% (IC_{50}) were determined. A typical assay involved a frozen stock solution of AChE from Electric Eel Type III (Sigma Chemical Co.-1000 units/1.1 mL) diluted to a working solution of 5 units/mL. 50 μL (0.25 units) was pipetted into a cuvette containing 100 μL of 0.01 M 5,5'-dithio*bis*(2-nitrobenzoic acid) (DTNB), 10-300 μL of inhibitor (depending on the final concentration required) and buffer solution (0.1 M sodium phosphate, pH 8) to make a total volume of 2980 μL. After a 15 min incubation period at room temperature, the cuvettes were placed in a Beckman Model 25 Spectrophotometer and 20 μL of substrate was added. The production of a yellow anion was followed spectrophotometrically at a wavelength of 412 nm for a 6 minute period.

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